UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/602,800 | 06/23/2000 | David B. Agus | P1760R1 | 1759 |

7590 02/13/2002

Darlby & Darby P.C
805 Third Avenue
New York, NY 10022

| EXAMINER |
|---|
| HUNT, JENNIFER ELIZABETH |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | 17 |

DATE MAILED: 02/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/602,800 | Applicant(s) AGUS ET AL.0 | |
|---|---|---|---|
| | Examiner Jennifer E Hunt | Art Unit 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *10-15,17,19 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,16,18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election without traverse of Group I, claims 1-10, 16, and 18-20 in Paper No. 9 is acknowledged. Further, applicant's election of the species (B), wherein the antibody is not conjugated to a cytotoxic compound, and (B) where the ErbB2 antibody is 2C4 is further acknowledged. These species were found in the art, and thus the search has not been extended.

2. Claims 1-21 are pending in the application. Claims 10-15, 17, 19, and 21 have been withdrawn from consideration: Claims 11-15, 17 and 21 are drawn to a non-elected invention Group, and claims 10 and 19 are drawn to a non-elected species of invention. Claims 1-9, 16, 18, and 20 are addressed herein.

### *Information Disclosure Statement*

3. The Information Disclosure Statement (PTO-1449) filed 1-29-2001 is acknowledged; however, copies of the references cited therein are not in the instant case. The examiner is making efforts to locate these references; however, resubmission of these documents, if possible, by applicant would facilitate their consideration and would be greatly appreciated by the examiner. A signed copy of the PTO-1449 will be mailed as soon as the examiner obtains copies of the references.

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-9, 16, 18 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating prostate cancer in mammals by administering the anti-HER2 antibody 2C4, does not reasonably provide enablement for a method of treating a human having prostate cancer or androgen dependent prostate cancer wherein the method comprises administering any anti-ErbB2 antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

Claim 1 is broadly drawn to a method of treating prostate cancer in a human by administering an antibody which binds ErbB2 and which further blocks activation of an ErbB receptor. Dependent claims 2, 4, and 5, respectively recite that the antibody blocks binding of 2C4, has a biological characteristic of 2C4, or comprises 2C4. Dependent claim 3 recites that the antibody blocks TGF-alpha activation of mitogen activated protein kinase (MAPK). Dependent claims 6 and 7 respectively recite that

the antibody is an antibody fragment, and that the fragment is an Fab fragment. Dependent claims 8 and 9 respectively recite that the antibody, and the antibody fragment is not conjugated to a cytotoxic agent. Claim 16 is drawn to a method of treating androgen dependent prostate cancer in a human by administering an antibody which binds ErbB2. Dependent claim 18 recites that the treatment results in an increased PSA index. Dependent claim 20 recites that the antibody comprises 2C4.

The specification teaches that administration of the monoclonal antibodies 2C4, 7C2, and HERCERPTIN ® (which is a humanized 4D5 antibody) each inhibits growth in androgen dependent prostate cancer in androgen dependent prostate cancer xenograft models (see pages 50-56). The specification further teaches that 2C4 but not HERCEPTIN ® is able to block TGF-alpha, HRG or EGF activation of MPAK. The specification further teaches that when HERCEPTIN ® is administered to androgen dependent prostate cancer xenograft models, PSA increases, even though tumor growth is inhibited.

The specification has not demonstrated the reproducible production of antibodies which have properties identical to 2C4 or HERCEPTIN ® nor of antibodies of other species origins which have the claimed properties. The production of a hybridoma which secretes a monoclonal antibody having a particular set of specifically defined characteristics is an unpredictable event. The specification fails to set forth the reproducibility of the generically claimed method of treatment using an antibody which binds ErbB2 and blocks any ErbB receptor, and further which blocks TGF-alpha activation of MAPK. In view of the unpredictability of producing antibodies

having the claimed properties from among the $10^6$- $10^{10}$ possible antibody variable region specificities encoded in the mammalian genome and in view of the lack of disclosure of the reproducibility of these antibodies, it does not appear that the antibodies required for the broadly claimed methods can be reproduced from the written disclosure alone. Further it is established in the art that antibodies to the ErbB2 receptor exhibit highly variant activity. For example, Xu et al., Int. J. Cancer, Vol. 53, pages 401-408, 1993 described a panel of 10 anti-HER2 Mab's which exhibit distinct binding characteristics and activities (see abstract). Also, Shepard et al., Journal of Clinical Immunology, Vol. 11, No. 3, 1991, pages 117-126 describes a panel of 9 anti-HER2 Mab's which exhibit distinct binding characteristics and activities (see pages 119-120.

The disclosure of one antibody which binds ErbB2 and blocks binding of one ErbB receptor to a single ligand is insufficient support under the first paragraph of 35 U.S.C 112 for claims which encompass any and all antibodies which bind ErbB2 and block binding by any ErbB ligand, including the specific interactions recited in the claims, and those yet undiscovered. The courts have held that:

"Inventor should be allowed to dominate future patentable inventions of others where those inventions were based In some way on his teachings, since some improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and hence, not In compliance with the first paragraph of U.S.C. 112; that paragraph

requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill In the art; In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement In the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; In cases involving unpredictable factors, such as chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."In re Fisher 427 F.2d 833, 166 USPQ 18 (CCPA 1970).

In the instant case, the degree of unpredictability of both antibody activity and treatment efficacy is high, as set forth above.

Further, with regard to claim 18, drawn to administration of an antibody which treats cancer, yet produces an increase in PSA there is no guidance or objective evidence that any antibody other than HERCEPTIN ® would produce this same effect. The treatment of prostate cancer and concurrent *rise* in PSA is counterintuitive from that which is known in art (where treatment efficacy is often gauged by measuring decreases in PSA), and applicant has not provided any guidance or objective evidence that such a rise might in any way correlate to the treatment administered, or further, that t might be reproducible, or even desirable with any anti ErbB2 antibody other than HERCEPTIN ®.

Therefore it would require undue experimentation to practice the invention commensurate in scope with the claims.

6. Claims 2, 4-5, and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not set forth in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification lacks complete deposit information for the deposit of the antibody 2C4. While the specification provides enough information for one of skill in the art to produce an antibody with the same or similar properties as 2C4, reproduction of an identical 2C4 is an unpredictable event. Because it does not appear that 2C4 is publicly available or can be reproducibly isolated from nature without undue experimentation and because certain of the claims specially require the use of 2C4, a suitable deposit of 2C4 for patent purposes is required or evidence must be provided that 2C4 is well known and readily available to the public.

Furthermore, unless the deposit was made at or before the time of filing, a declaration filed under the 37 C.F.R. 1/132 is necessary to construct a chain of custody. The declaration, executed by a person in a position to know, should identify the deposited antibody by its depository accession number, establish that the deposited antibody is the same as that described in the specification, and establish that the deposited antibody was in applicant's possession at the time of filing. See In re Lundak, 773 F.2d. 1216, 227 U.S.P.?Q. 90 (Fed. Cir. 1985).

It is not clear from the disclosure that deposits of 2C4 meet all the criteria set forth in MPEP 608/01 (p)(C), items 1-3. Assurance of compliance may be in the form

of a declaration or averment under oath. A suggested format for such a declaration or averment is outlined below:

SUGGESTION FOR DEPOSIT OF BIOLOGICAL MATERIAL

A declaration by applicant, assignee, or applicant's agent identifying a deposit of biological material and averring the following may be sufficient to overcome an objection and rejection based on a lack of availability of biological material.

1. Identifies declarant.
2. States that a deposit of the material has been made in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted. The depository is to be identified by name and address.
3. States that the deposited material has been accorded a specific (recited) accession number.
4. States that all restrictions on the availability to the public of the material will be irrevocably removed upon the granting of a patent.
5. States that the material has been deposited under conditions that ensure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 35 CFR 1.14 and 35 USC 122.
6. States that the deposited material will be stored with all care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case at least thirty (30) years after the date of a deposit or for the enforceable life of the patent, whichever is longer.
7. Acknowledges the duty to replace the deposit should the depository be unable to furnish a sample when requested due to the condition of the deposit.
8. That he/she declares further that all statements made therein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Additionally, the deposit must be referred to in the body of the specification and be identified by deposit (accession) number, name and address of the depository, and the complete taxonomic description.

As a possible means of completing the record, applicants may submit a copy of the deposit receipt.

*Claim Rejections - 35 USC § 102*

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

8. Claims 1 and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Greene et al., US Patent 5,842,311, published October 20, 1998, or Arakawa et al., US Patent 5,783,186, published July 21, 1998.

Greene et al., US Patent 5,842,311 teaches a method of treating a patient, which includes humans, by administering an antibody which binds ErbB2 and blocks activation of an ErbB receptor. Specifically, Greene teaches that the p185 oncogene (which is the same as ErbB2) has been found active in prostate adenocarcinoma, and

further provides a method of using monoclonal antibodies which bind to ErbB2 to treat mammalian cancer tumors which express a translation of the neu oncogene on their surfaces (see column 3, line 50-column 5). The antibody of Greene et al. is not conjugated to a cytotoxic compound.

Arakawa et al., US Patent 5,842,311 teaches a method of treating a patient, which includes humans, by administering an antibody which binds ErbB2 and blocks activation of an ErbB receptor. Specifically, Arakawa teaches that the HER2 oncogene (which is the same as ErbB2) has been found active in prostate adenocarcinoma, and further provides a method of using monoclonal antibodies which bind to ErbB2 to treat mammalian cancer tumors which express HER2 on their surfaces (see column 6, lines 12-17, and lines 53-59). The antibody of Arakawa et al. is not conjugated to a cytotoxic compound.

9. Claims 1, 8 and 16 are rejected under 35 U.S.C. 102(e) as being anticipated by Greene et al., US Patent 5,842,311, published October 20, 1998, or Arakawa et al., US Patent 5,783,186, published July 21, 1998, as evidenced by Murphy et al., The American Society Textbook of Clinical Oncology, 1995, pages 126-127.

Greene et al., US Patent 5,842,311 teaches a method of treating a patient, which includes humans, by administering an antibody which binds ErbB2 and blocks activation of an ErbB receptor. Specifically, Greene teaches that the p185 oncogene (which is the same as ErbB2) have been found active in prostate adenocarcinoma, and further provides a method of using monoclonal antibodies which bind to ErbB2 to

treat mammalian cancer tumors which express a translation of the neu oncogene on their surfaces (see column 3, line 50-column 5). The antibody of Greene et al. is not conjugated to a cytotoxic compound.

Arakawa et al., US Patent 5,842,311 teaches a method of treating a patient, which includes humans, by administering an antibody which binds ErbB2 and blocks activation of an ErbB receptor. Specifically, Arakawa teaches that the HER2 oncogene (which is the same as ErbB2) has been found active in prostate adenocarcinoma, and further provides a method of using monoclonal antibodies which bind to ErbB2 to treat mammalian cancer tumors which express HER2 on their surfaces (see column 6, lines 12-17, and lines 53-59). The antibody of Arakawa et al. is not conjugated to a cytotoxic compound.

The term "prostate cancer" generally refers to androgen dependent prostate cancer, as evidenced by Murphy et al., page 127, first column.

10. Claims 1, 6, and 8-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Curnow, Cancer Immunology Immunotherapy, Vol. 45, pages 210-215, 1997.

Curnow teaches a method of treating a human patient by administering an antibody which binds ErbB2 and blocks activation of an ErbB receptor (MDX-H210). The MDX-H210 antibody is not conjugated to a cytotoxic compound (see page 210, column 2).

11. Claims 1, 6, 8-9, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Curnow, Cancer Immunology Immunotherapy, Vol. 45, pages 210-215, 1997, as evidenced by Murphy et al., The American Society Textbook of Clinical Oncology, 1995, pages 126-127.

Curnow teaches a method of treating a human patient by administering an antibody which binds ErbB2 and blocks activation of an ErbB receptor (MDX-H210). The MDX-H210 antibody is not conjugated to a cytotoxic compound (see page 210, column 2). The term "prostate cancer" generally refers to androgen dependent prostate cancer, as evidenced by Murphy et al., page 127, first column.

***Claim Rejections - 35 USC § 103***

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudziak et al., US Patent 5,725,856, published March 10, 1998, in view of Zhi, Dissertation Abstracts, Vol. 55, No. 11, page 4738-B, May 1995.

Hudziak et al., US Patent 5,842,311 teaches a method of treating a patient, which includes humans, by administering an antibody which binds ErbB2 and blocks

activation of an ErbB receptor. Specifically, Hudziak teaches that the HER2 oncogene (which is the same as ErbB2) has been found active in numerous cancers, and further provides a method of using monoclonal antibodies which bind to ErbB2 to treat mammalian cancer tumors which express HER2 on their surfaces (see column 4, lines 27-31, column 6, lines 31-35, column 8, lines 27-30, column 10, lines 46-53, column 11, lines 32-40). The antibody of Hudziak et al. is not conjugated to a cytotoxic compound.

Hudziak et al. fails to teach that prostate cancer overexpresses HER2.

Zhi teaches that prostate cancer overexpresses HER2.

Therefore it would be *prima facie* obvious to one of ordinary skill in the art at the time of applicant's invention to use the method of treating HER2 overexpressing cancers on prostate cancer, and one would have been motivated to do so because prostate cancer overexpresses HER2 and anti-HER2 antibodies are an effective treatment for HER2 positive cancer, as taught by Hudziak et al.

14. Claims 1, 8, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudziak et al., US Patent 5,725,856, published March 10, 1998, as evidenced by Murphy et al., The American Society Textbook of Clinical Oncology, 1995, pages 126-127, in view of in view of Zhi, Dissertation Abstracts, Vol. 55, No. 11, page 4738-B, May 1995.

Hudziak et al., US Patent 5,842,311 teaches a method of treating a patient, which includes humans, by administering an antibody which binds ErbB2 and blocks

activation of an ErbB receptor. Specifically, Hudziak teaches that the HER2 oncogene (which is the same as ErbB2) has been found active in numerous cancers, and further provides a method of using monoclonal antibodies which bind to ErbB2 to treat mammalian cancer tumors which express HER2 on their surfaces (see column 4, lines 27-31, column 6, lines 31-35, column 8, lines 27-30, column 10, lines 46-53, column 11, lines 32-40). The antibody of Hudziak et al. is not conjugated to a cytotoxic compound. The term "prostate cancer" generally refers to androgen dependent prostate cancer, as evidenced by Murphy et al., page 127, first column.

Hudziak et al. fails to teach that prostate cancer overexpresses HER2.

Zhi teaches that prostate cancer overexpresses HER2.

Therefore it would be *prima facie* obvious to one of ordinary skill in the art at the time of applicant's invention to use the method of treating HER2 overexpressing cancers on prostate cancer, and one would have been motivated to do so because prostate cancer overexpresses HER2 and anti-HER2 antibodies are an effective treatment for HER2 positive cancer, as taught by Hudziak et al.

15. Claims 1, 8, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhi, Dissertation Abstracts, Vol. 55, No. 11, page 4738-B, May 1995, in view of Baselga et al., Oncology, Suppl. 2, March 1997 (Baselga I), or Baselga et al., Journal of Clinical Oncology, Vol. 14, No. 3, pages 737-744, March 1996 (Baselga II).

Zhi teaches a method of treating a prostate cancer cells, by administering an antibody which binds ErbB2 and blocks activation of an ErbB receptor in a prostate

cancer which is androgen dependent. The antibody of Zhi is not conjugated to a cytotoxic compound. (see entire abstract)

Zhi fails to teach treatment of humans.

Baselga I teaches a method of treatment of a human patient diagnosed with a disorder characterized by over expression of ErbB2 receptor comprising administering an effective amount of an anti-ErbB2 antibody which binds the HER2 extracellular domain (page 46).

Baselga II teaches a method of treatment of a human patient diagnosed with a disorder characterized by over expression of ErbB2 receptor comprising administering an effective amount of an anti-ErbB2 antibody which binds the HER2 extracellular domain (see for example, abstract).

Therefore it would be *prima facie* obvious to one of ordinary skill in the art at the time of applicant's invention to use the method of treating HER2 overexpressing prostate cancer cells to treat humans having prostate cancer, and one would have been motivated to do so because anti-HER2 antibodies function in vitro to treat prostate cancer cells, as taught by Zhi, and further are an effective treatment for humans having a HER2 positive cancer, as taught by Baselga I and Baselga II.

16. Claims 1-5, 8, 16, and 20 are rejected under 35 U.S.C. 103(a) as being anticipated by Greene et al., US Patent 5,842,311, published October 20, 1998, or Arakawa et al., US Patent 5,783,186, published July 21, 1998, as evidenced by Murphy et al., The American Society Textbook of Clinical Oncology, 1995, pages 126-127, in

view of Fendly et al., Cancer Research, Vol. 50, pages 1550-1558, March 1, 1990, or Shepard et al., Journal of Clinical Immunology, Vol. 11, No. 9, pages 117-126, 1991.

Greene et al., Arakawa et al., and Murphy et al. teach as applied to claims 1, 8, and 16 supra.

Greene et al., and Arakawa et al. fail to teach and antibody which blocks binding of 2C4 or the specific monoclonal antibody 2C4, or an antibody which blocks TGF-alpha activation of MAPK.

Fendly et al. teaches the monoclonal antibody 2C4, and that the antibody selectively binds HER2 (see for example, page 1552). While Fendly et al. does not explicitly recite that 2C4 blocks TGF-alpha activation of MAPK, this would be an inherent characteristic of the antibody.

Shepard et al. teaches the monoclonal antibody 2C4, and that the antibody selectively binds HER2 and is capable of treating HER2 positive cells line (see for example, page 123). While Shepard et al. does not explicitly recite that 2C4 blocks TGF-alpha activation of MAPK, this would be an inherent characteristic of the antibody.

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the 2C4 antibodies of Fendly et al. and Shepard et al., in the methods of Greene et al., or Arakawa et al., and one would have been motivated to do so because these antibodies selectively bind to HER2 and are able to treat cells which overexpress HER2, as taught by Fendly et al., and Shepard et al.

17. Claims 1-6, 8-9, 16 and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Curnow, Cancer Immunology Immunotherapy, Vol. 45, pages 210-215, 1997, as evidenced by Murphy et al., The American Society Textbook of Clinical Oncology, 1995, pages 126-127 in view of Fendly et al., Cancer Research, Vol. 50, pages 1550-1558, March 1, 1990, or Shepard et al., Journal of Clinical Immunology, Vol. 11, No. 9, pages 117-126, 1991.

Curnow teaches as applied to claims 1, 6, 8-9, and 16 supra.

Curnow fails to teach and antibody which blocks binding of 2C4 or the specific monoclonal antibody 2C4, or an antibody which blocks TGF-alpha activation of MAPK.

Fendly et al. teaches the monoclonal antibody 2C4, and that the antibody selectively binds HER2 (see for example, page 1552). While Fendly et al. does not explicitly recite that 2C4 blocks TGF-alpha activation of MAPK, this would be an inherent characteristic of the antibody.

Shepard et al. teaches the monoclonal antibody 2C4, and that the antibody selectively binds HER2 and is capable of treating HER2 positive cells line (see for example, page 123). While Shepard et al. does not explicitly recite that 2C4 blocks TGF-alpha activation of MAPK, this would be an inherent characteristic of the antibody.

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the 2C4 antibodies of Fendly et al. and Shepard et al., in the method of Curnow one would have been motivated to do so

because these antibodies selectively bind to HER2 and are able to treat cells which overexpress HER2, as taught by Fendly et al., and Shepard et al.

18. Claims 1-5, 8, 16, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudziak et al., US Patent 5,725,856, published March 10, 1998, as evidenced by Murphy et al., The American Society Textbook of Clinical Oncology, 1995, pages 126-127, in view of in view of Zhi, Dissertation Abstracts, Vol. 55, No. 11, page 4738-B, May 1995, in view of Fendly et al., Cancer Research, Vol. 50, pages 1550-1558, March 1, 1990, or Shepard et al., Journal of Clinical Immunology, Vol. 11, No. 9, pages 117-126, 1991.

Hudziak et al., Murphy et al., and Zhi teach as applied to claims 1, 8, and 16 supra. Hudziak et al., Murphy et al., and Zhi fail to teach and antibody which blocks binding of 2C4 or the specific monoclonal antibody 2C4, or an antibody which blocks TGF-alpha activation of MAPK.

Fendly et al. teaches the monoclonal antibody 2C4, and that the antibody selectively binds HER2 (see for example, page 1552). While Fendly et al. does not explicitly recite that 2C4 blocks TGF-alpha activation of MAPK, this would be an inherent characteristic of the antibody.

Shepard et al. teaches the monoclonal antibody 2C4, and that the antibody selectively binds HER2 and is capable of treating HER2 positive cells line (see for example, page 123). While Shepard et al. does not explicitly recite that 2C4 blocks

TGF-alpha activation of MAPK, this would be an inherent characteristic of the antibody.

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the 2C4 antibodies of Fendly et al. and Shepard et al., in the method of Hudziak et al., Murphy et al., and Zhi one would have been motivated to do so because these antibodies selectively bind to HER2 and are able to treat cells which overexpress HER2, as taught by Fendly et al., and Shepard et al.

19. Claims 1-5, 8, 16, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhi, Dissertation Abstracts, Vol. 55, No. 11, page 4738-B, May 1995, in view of Baselga et al., Oncology, Suppl. 2, March 1997 (Baselga I), or Baselga et al., Journal of Clinical Oncology, Vol. 14, No. 3, pages 737-744, March 1996 (Baselga II) in view of Fendly et al., Cancer Research, Vol. 50, pages 1550-1558, March 1, 1990, or Shepard et al., Journal of Clinical Immunology, Vol. 11, No. 9, pages 117-126, 1991.

Zhi, Baselga I, and Baselga II teach as applied to claims 1, 8, and 16 supra. Zhi, Baselga I, and Baselga II fail to teach and antibody which blocks binding of 2C4 or the specific monoclonal antibody 2C4, or an antibody which blocks TGF-alpha activation of MAPK.

Fendly et al. teaches the monoclonal antibody 2C4, and that the antibody selectively binds HER2 (see for example, page 1552). While Fendly et al. does not

explicitly recite that 2C4 blocks TGF-alpha activation of MAPK, this would be an inherent characteristic of the antibody.

Shepard et al. teaches the monoclonal antibody 2C4, and that the antibody selectively binds HER2 and is capable of treating HER2 positive cells line (see for example, page 123). While Shepard et al. does not explicitly recite that 2C4 blocks TGF-alpha activation of MAPK, this would be an inherent characteristic of the antibody.

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the 2C4 antibodies of Fendly et al. and Shepard et al., and in the method of Zhi, Baselga I, and Baselga II one would have been motivated to do so because these antibodies selectively bind to HER2 and are able to treat cells which overexpress HER2, as taught by Fendly et al., and Shepard et al.

20. Claims 1-9, 16 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greene et al., US Patent 5,842,311, published October 20, 1998, or Arakawa et al., US Patent 5,783,186, published July 21, 1998, or Curnow, Cancer Immunology Immunotherapy, Vol. 45, pages 210-215, 1997, or Hudziak et al., US Patent 5,725,856, published March 10, 1998, or Zhi, Dissertation Abstracts, Vol. 55, No. 11, page 4738-B, May 1995, or Baselga et al., Oncology, Suppl. 2, March 1997 (Baselga I), or Baselga et al., Journal of Clinical Oncology, Vol. 14, No. 3, pages 737-744, March 1996 (Baselga II), all further in view of Fendly et al., Cancer Research,

Vol. 50, pages 1550-1558, March 1, 1990, or Shepard et al., Journal of Clinical Immunology, Vol. 11, No. 9, pages 117-126, 1991, all in view of Schlom, Molecular Foundations of Oncology, pages 95-134, 1991.

Greene et al., or Arakawa et al., or Curnow, or Hudziak et al., or Zhi, or (Baselga I), or (Baselga II), or Fendly et al., or Shepard et al., teach as applied to claims 1-6, 8-9, 16 and 20 supra. Greene et al., or Arakawa et al., or Curnow, or Hudziak et al., or Zhi, or (Baselga I), or (Baselga II), or Fendly et al., or Shepard et al., fail to teach antibody fragments, including Fab's.

Schlom described the various known antibody modifications, including Fab's and that they provide the therapeutic advantage of reducing the host anti-Mab response (see pages 112-123).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the Fab's of Schlom in the methods of Greene et al., or Arakawa et al., or Curnow, or Hudziak et al., or Zhi, or (Baselga I), or (Baselga II), or Fendly et al., or Shepard et al., and one would have been motivated to do so because they reduce the host anti-Mab response.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E Hunt whose telephone number is (703) 308-7548. The examiner can normally be reached on Monday-Friday, 6-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-0196.

Jennifer E Hunt
Examiner
Art Unit 1642

jeh
February 11, 2002

SHEELA HUFF
PRIMARY EXAMINER